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# Saccadic eye movements in juvenile variant of Huntington disease

Natalia Grabska [a,*], Monika Rudzińska [b], Magdalena Wójcik-Pędziwiatr [a], Michał Michalski [a], Jarosław Sławek [c,d], Andrzej Szczudlik [a]

[a] Department of Neurology, Jagiellonian University Medical College, Krakow, Poland
[b] Department of Neurology, Medical University of Silesia, Katowice, Poland
[c] Department of Neurology, St. Adalbert Hospital, Gdansk, Poland
[d] Department of Neurological and Psychiatric Nursing, Medical University of Gdansk, Gdańsk, Poland

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ABSTRACT

*Background and purpose:* Huntington disease (HD) is a neurodegenerative disease leading to involuntary movements, cognitive and behavior decline. The juvenile variant of HD (JHD) manifests in people younger than 21 and is characterized by a different clinical presentation, i.e. rigidity and bradykinesia. Rapid eye movements were not extensively studied in patients with JHD. Aims of our study were to describe the saccadic eye movements in JHD patients and to find a correlation between the saccade abnormalities, severity of the disease and cognitive and behavior deterioration.

*Materials and methods:* We studied 10 patients with JHD and 10 healthy subjects. Reflexive and volitional saccades were assessed with the Saccadometer Advanced. The battery of cognitive and behavior tests was performed as well.

*Results:* We found a prolonged latency, slowness and decreased velocity of reflexive and voluntary saccades and reduced amplitude of voluntary saccades. Moreover, patients with JHD executed a significantly lower number of volitional saccades and made more incorrect cued saccades than controls. We noted a significant correlation between prolonged latency of reflexive saccades with gap task and disease severity and significant inverse correlation between prolonged latency of reflexive saccades with overlap task, an increased number of incorrect saccades made on a cue and impairment in working memory.

*Conclusion:* Abnormalities of saccade eye movements in patients with JHD were similar to those reported in patients with HD. Our findings did not confirm abnormalities previously reported in patients with early onset HD. Abnormal saccade parameters correlated also with a disease severity and cognitive deterioration.



* *Corresponding author at*: Department of Neurology, University Hospital, Jagiellonian University Medical College, Krakow, ul. Botaniczna 3, 31-503 Kraków, Poland. Tel.: +48 124248600; fax: +48 124248626.
E-mail address: nath87@wp.pl (N. Grabska).

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## 1. Introduction

Huntington disease (HD) is a progressive, neurodegenerative disease, caused by the expanded number of CAG repeats in huntingtin gene on the chromosome 4. Mean age of disease onset is 40 years [1]. In almost 5% of cases [2], disease begins before the age of 21 and is called as juvenile HD (JHD) [3]. JHD is commonly characterized by similar clinical symptoms as HD but rigidity, bradykinesia and dystonia are more prominent than chorea. However, in some cases, early – onset HD, known as Westphal variant, manifests with rigidity and hypokinesia without choreatic movements [4].

Saccades are fast movements of eyes, generated in regard to a fast shift of an animated signal. Saccades could be triggered automatically, in response to suddenly appearing visual stimulus (reflexive saccades), or internally initiated, either on a command or to remembered location of a target (voluntary saccades). Impairment of saccadic eye movements reflects pathological changes in brain and therefore is a useful tool for assessing and tracking various neurological disorders, especially neurodegenerative diseases [5].

Saccade impairments have long been described in HD. At the beginning of disease, patients show deficits of volitional saccades, especially increased latency and hypometric amplitude of saccades. Additionally, they are unable to suppress reflexive saccades to a suddenly appearing visual target. With a disease progression, slowness of volitional saccades and abnormalities of reflexive saccades such as prolonged latency, slowness and hypometria, are detected [5–9]. Saccade impairments in JHD patients were described roughly and only in case reports [10]. Lasker et al. [11] compared patients who developed HD before and after the age of 30 and noted some differences between these two groups. In patients with early onset of symptoms we frequently observed problems with saccades' amplitude and saccades with smaller amplitude. In contrast, patients who developed symptoms later, presented difficulties with saccades' initiation and made saccades with increased latency.

The aim of the study was to assess the saccadic eye movement abnormalities in patients with JHD, as compared to the healthy controls, and to determine the relation between saccade impairments and disease severity and the cognitive and behavioral findings.

## 2. Materials and methods

The involvement to the study was proposed to all patients with genetically confirmed JHD who participated in the study 'REGISTRY' conducted by the European Huntington Disease Network in Krakow and Gdansk between 2008 and 2010. Eight patients remained under the care of Krakow Center and 2 were recruited from patients from Gdansk. Controls were recruited from medical students and their relatives. They were matched to the patients with the age (±5 years) and sex. The control subjects were interviewed paying special attention to the neurological disorders, as well as their family history; the number of CAG repeats was not determined. All participants provided informed consent to participate in the study.

Exclusion criteria were as follows: restriction of the eyes motility, scotomy, severe refraction abnormalities, red or green color blindness, other diseases of nervous system or muscles which cause oculomotor abnormalities, use of medications which influence the eye movements except for propranolol and primidone, alcohol or drug abuse, endured intoxication by drugs, carbon monoxide or other chemical agent, symptomatic hypo- or hyperthyroidism, autoimmune disease, malignancy, severe cardiac, renal, hepatic or pulmonary insufficiency.

The interview concerning demographic and clinical data was obtained from each patient and family member who took care of the patient. During the interview we also collected information about ophthalmological diseases Neurological examination and laboratory tests (including thyroid stimulating hormone and ceruloplasmine) were performed in all patients. Severity of disease was assessed by the Clinical Global Impression (CGI) 7-point scale (1 – without symptoms, 2 – slight symptoms, 3 – mildly ill, 4 – moderately ill, 5 – markedly ill, 6 – severely ill, 7 – extremely ill).

Severity of motor signs was assessed using the motor part of the United Huntington's Disease Rating Scale (UHDRS) [12]. Severity of depression symptoms was assessed by the Beck Depression Inventory (BDI) [13] and the Hamilton scale [14]. Behavioral characteristics of patients were assessed using the Problem Behaviors Assessment for Huntington's Disease – short version (PBA-s) [15]. Patients were also checked by a cognitive battery, consisted of three domains which are part of UHDRS scale and assessing prefrontal functions: the Symbol Digit Modality Test (SDMT) [16], the Stroop Color Word Test (SCWT) [17] and the Verbal Fluency Test (VFT, one category and three letters) [18].

The eye movements were recorded using Saccadometer Advanced (Ober Consulting, Poland). It comprises four light-emitting diodes: two (one green and one red) located in central position and two others 10 degrees bilaterally, which enable to examine visually-guided saccades [19]. The examinations were made in a soundproof and darkened room. The apparatus was mounted on the subject's head, which prevented the influence of head movements on the saccade recording. Each participant was asked to sit at a fixed distance of 100 cm from a screen, on which the light targets were projected and to follow with their eyes the red laser dots according to the instruction given by the investigator. We investigated 10- and 20-degree reflexive saccades, 20-degree pace-induced saccades, where subject was asked to look alternately at continuously illuminated two light dots as quickly as possible within 30 s and 10-degree cued saccades, where task instruction ('look at right or left visual stimulus') was indicated by the color of the central light cue. Additionally, latencies of reflexive saccades were assessed with gap and overlap paradigm. In the gap paradigm, there was 200-ms pause between disappearance of central fixation target and appearance of the peripheral one. For each task, except pace-induced saccades, sixty experimental trials were performed. All tasks were preceded by 20 calibration trials. Ten-degree reflexive saccades were assessed for latency. Twenty-degree reflexive saccades were used for evaluation of amplitude, duration and velocity. In the gap and overlap paradigm, only the latency were assessed. The comparison between the mean

latency in reflexive, gap and overlap paradigms was performed. For pace-induced saccades, we evaluated number of saccades, latency, amplitude, velocity and duration. In cued saccades, we evaluated also a distractibility index (incorrect saccades/number of trials) and the latency of correct and incorrect saccades. Incorrect saccade meant saccade executed in an inappropriate direction, i.e. against the cue.

### 2.1. *Statistical analyses*

Numerical variables were characterized by mean values with standard deviation (SD). Significance of differences between groups regarding numerical variables was assessed using the Mann–Whitney *U*-test. The Pearson rank correlation coefficient was used to assess relation between numerical variables. All statistical analyses were conducted using commercial statistical software STATISTICA (data analysis software system), StatSoft, Inc. (2011), version 10 licensed to the Jagiellonian University.

## 3. Results

All ten JHD patients registered in the study 'REGISTRY' agreed to participate. The demographic and clinical data of the patients are provided in Table 1. The control group did not differ significantly from patients in relation to the mean age at the examination ($30.5 \pm 4.6$ years in the control group vs. $27.2 \pm 3.2$ in JHD group, $p > 0.05$) and sex (4 females and 6 males in both groups). The duration of a disease was $8.5 \pm 2.9$ (range: 4–12 years). There were three patients with paternally transmitted disease and seven cases with maternal disease transmission. The age of onset in patients with paternally transmitted disease ($18.3 \pm 2.5$ years) did not differ from patients with maternally inherited disease ($18.8 \pm 1.3$ years). All patients' symptoms are listed in Table 2. At the time of examination, 80% patients manifested chorea, 80% slowness and bradykinesia, 70% rigidity. Other symptoms were: wide-based gait (80%), dystonia (50%), and dysarthria (50%). All patients developed psychiatric disturbances, including depression (60%), suicidal ideation (20%), suicidal attempt (10%), perseverative and obsessive behaviors (10%). Irritability, violent or aggressive behavior and apathy were a part of a clinical presentation in 60% of patients. Cognitive decline was observed in 40%. Two patients manifested typical Westphal variant. Results of clinical scales are summarized in Table 3.

The comparisons of the mean values of the most important saccade parameters in the JHD patients and in the control group are summarized in Table 3. Patients with JHD differed significantly ($p < 0.05$) from the control group for the mean latency, velocity and duration of reflexive saccades and for the mean latency in the gap and overlap paradigms. Reflexive saccades in JHD patients were nearly two times slower and their mean duration was prolonged. Initiation of rapid eye movements in reflexive saccades, as well as in gap and overlap tasks, were increased. The mean difference in the latency between the gap and overlap paradigms was 2.1 ms ($p = 0.11$) in JHD patients compared to 74.5 ms ($p = 0.008$) in controls. No changes between patients and control groups in the amplitude for reflexive saccades were found (Table 4).

Comparison of the mean values of the latency, velocity, amplitude and duration of volitional saccades revealed significant differences between JHD and control groups in all these parameters. The mean latency was almost three times greater in JHD patients; saccades were slower and their duration was nearly two times prolonged. The mean amplitude was decreased, indicating that executed saccades were hypometric. Furthermore, the number of volitional saccades in JHD patients was significantly lower with the value of 28.6 saccades compared to the value of 54 executed saccades in control group ($p < 0.05$).

In the cued saccades task, 90% of JHD patients made more than 20% incorrect saccades, compared to control group where no one performed more than 20% incorrect responses. The distractibility index was significantly greater in JHD group in comparison to control ($47.423 \pm 16.36\%$ vs. $12.19 \pm 4.21\%$; $p < 0.001$). In addition, the mean latency of the correct and incorrect answers were significantly prolonged in JHD

**Table 1 – Demographic and clinical characteristics of studied patients.**

| Subject number | Gender (F/M) | Age at examination (years) | Age of HD onset (years) | Disease duration (years) | CAG repeats | Inheritance (M/P) |
|---|---|---|---|---|---|---|
| 1 | F | 25 | 16 | 9 | 62 | P |
| 2 | M | 26 | 18 | 8 | 55 | P |
| 3 | F | 30 | 18 | 12 | 50 | M |
| 4 | M | 27 | 20 | 7 | 56 | M |
| 5 | M | 29 | 19 | 10 | 61 | M |
| 6 | F | 25 | 21 | 4 | 53 | M |
| 7 | M | 23 | 17 | 6 | 55 | M |
| 8 | M | 30 | 18 | 12 | 52 | M |
| 9 | M | 33 | 21 | 12 | 53 | P |
| 10 | F | 24 | 19 | 5 | 59 | M |
| Mean ± SD or proportion | 4/6 | $27.2 \pm 3.2$ | $18.7 \pm 1.6$ | $8.5 \pm 2.99$ | $55.6 \pm 3.9$ | 7/3 |

F – female; M – male; HD – Huntington disease; P – paternal; M – maternal; SD – standard deviation.

**Table 2 – Clinical manifestation.**

| Subject number | Main symptoms | Clinical diagnosis |
|---|---|---|
| 1 | Rigidity, slowness, bradykinesia, dysathria, wide-base gait, irritability/aggressive behavior, depression, cognitive impairment | Westphal variant |
| 2 | Chorea, slowness, dystonia, rigidity, dysathria, wide-base gait, suicidal ideation | JHD |
| 3 | Chorea, slowness, bradykinesia, dysathria, wide-base gait, irritability/aggressive behavior | JHD |
| 4 | Chorea, dystonia, slowness, bradykinesia, rigidity, wide-base gait, depression, irritability/aggressive behavior, cognitive impairment | JHD |
| 5 | Chorea, dystonia, slowness, bradykinesia, rigidity, dysathria, wide-base gait, depression, suicidal attempt, suicidal ideation, irritability/aggressive behavior | JHD |
| 6 | Bradykinesia, chorea, rigidity | JHD |
| 7 | Slowness, bradykinesia, rigidity, dysathria, wide-base gait, depression, cognitive impairment | Westphal variant |
| 8 | Chorea, dystonia, slowness, bradykinesia, slowness, wide-base gait, depression, irritability/aggressive behavior, obsessive–compulsive behavior, cognitive impairment | JHD |
| 9 | Chorea, slowness, bradykinesia, rigidity, dystonia, wide-base gait, depression | JHD |
| 10 | Chorea, irritability/aggressive behavior | JHD |

patients. There was no significant correlation between the distractibility index and the latency of correct or incorrect saccades in each JHD and control group. Furthermore, in JHD group, the mean latency of incorrect saccades was higher than that of correct saccades. In healthy subjects, the mean latency of incorrect responses was lower than that of correctly performed saccades.

Analysis of saccades parameters in relation to disease severity and other clinical features revealed that the mean latency of reflexive saccades with gap in JHD patients increased significantly with the increase in UHDRS motor score ($r = 0.76$, $p = 0.019$). The inverse correlation was found between median latency of reflexive saccades with overlap and results of VFT ($r = -0.703$, $p < 0.05$) and also between distractibility index and VFT results ($r = -0.658$, $p < 0.05$). Increased latency of reflexive saccades and increased number of incorrect saccades significantly correlated with decreased number of listed words in VFT. We did not find any other significant correlation between saccadic measures and results of Hamilton and Beck scales, SDMT and SCWT tests and behavioral assessment.

## 4. Discussion

This is the first study of the saccadic eye movement in the group of JHD patients as compared to control group. We have found that JHD patients have prolonged latency and decreased velocity of reflexive and volitional saccades, lower amplitude (hypometric) of volitional saccades, significantly lower number of executed, volitional saccades and increased number of incorrect saccades made on a cue. Our results are on line with previous reports separately showing slowness of reflexive and volitional saccades, problems with the saccade initiation compensated for turning the head in the direction of light target or frequent eye blinks [10], hypometric volitional saccades and increased number of incorrect responses in saccades made on a cue [9].

Our study do not confirm the previous findings reported by Lasker et al. [11] that early-onset (before 30 years of age) HD patients have prolonged latency of volitional saccades only. We found that both latency and velocity were decreased in reflexive and volitional saccades in JHD. The difference in

**Table 3 – Results of motor, behavior and cognitive assessment.**

| Subject number | UHDRS | Beck Depression Inventory | Hamilton Scale | CGI | SDMT | SCWT | VFT | PBA-s |
|---|---|---|---|---|---|---|---|---|
| 1 | 51 | 5 | 0 | 5 | 12 | 80 | 22 | 2 |
| 2 | 46 | 20 | 10 | 5 | 12 | 57 | 10 | 33 |
| 3 | 35 | 6 | 0 | 4 | 20 | 127 | 12 | 0 |
| 4 | 38 | 24 | 22 | 4 | 15 | 92 | 16 | 43 |
| 5 | 72 | 40 | 29 | 6 | 11 | 37 | 13 | 59 |
| 6 | 6 | 0 | 0 | 1 | 23 | 193 | 32 | 0 |
| 7 | 25 | 24 | 16 | 4 | 29 | 125 | 25 | 35 |
| 8 | 24 | 26 | 21 | 5 | 11 | 74 | 16 | 27 |
| 9 | 28 | 34 | 13 | 3 | 16 | 89 | 13 | 15 |
| 10 | 2 | 0 | 0 | 2 | 46 | 176 | 32 | 7 |
| Mean ± SD | 32.7 ± 20.9 | 17.9 ± 14.3 | 11.1 ± 10.9 | 3.9 ± 1.5 | 19.5 ± 11.03 | 105 ± 50.12 | 19.1 ± 8.18 | 22.1 ± 20.5 |

UHDRS – Unified Huntington's Disease Rating Scale; CGI – Clinical Global Impression; SDMT – Symbol Digit Modality Test, SCWT – Stroop Color Word Test, VFT – Verbal Fluency Test, PBA-s – Problem Behaviors Assessment for Huntington's Disease – short version; SD – standard deviation.

**Table 4 – Latency, velocity, amplitude and duration of saccades in juvenile Huntington disease (JHD) patients and the control group: comparison of the reflexive saccades, volitional saccades, gap and overlap paradigm as well as cued saccades (data shown as means ± standard deviations).**

| | JHD group | Control group | *p*-Value |
|---|---|---|---|
| Latency (ms) | | | |
| Reflexive saccades | 321.44 ± 136.2 | 175.9 ± 19.8 | 0.020 |
| Volitional saccades | 1235.2 ± 1005.7 | 432.0 ± 185.9 | 0.001 |
| Gap | 398.3 ± 290.9 | 141.9 ± 20.7 | 0.006 |
| Overlap | 400.4 ± 147.7 | 215.4 ± 29.1 | 0.001 |
| Velocity (deg/s) | | | |
| Reflexive saccades | 347 ± 88.9 | 503.9 ± 66.9 | 0.001 |
| Volitional saccades | 368.2 ± 133.0 | 556.4 ± 278.1 | 0.025 |
| Amplitude (deg) | | | |
| Reflexive saccades | 18.6 ± 4.7 | 19.0 ± 2.0 | 0.54 |
| Volitional saccades | 17.1 ± 3.9 | 19.8 ± 7.4 | 0.049 |
| Duration (ms) | | | |
| Reflexive saccades | 73.1 ± 12.5 | 115.1 ± 37.5 | 0.002 |
| Volitional saccades | 113.4 ± 28.9 | 63.5 ± 24.5 | 0.001 |
| Cued saccades latency (ms) | | | |
| Correct | 661.3 ± 147.9 | 408.1 ± 55.7 | 0.003 |
| Incorrect | 670.3 ± 185.7 | 366.7 ± 57.5 | 0.003 |

results could be related to difference in the age and disease duration of the patients in both studies. Our patients were significantly younger at the onset of HD but they were studied after longer time of disease duration than patients in the study by Lasker et al.

Although our patients presented symptoms typical for parkinsonism, saccade impairments in JHD differed from those reported in Parkinson disease (PD), where a saccade hypometria is predominantly observed and saccade slowness and prolonged initiation developed at the advanced stage of PD [5,20]. It emphasizes the different pathological processes in these two diseases. According to already reported studies, the pathology of two distinct pathways within the basal ganglia contributes to the rigidity and akinesia, and also the most prominent saccades abnormality, i.e. prolonged initiation [1,21]. However, other factors may play a role in the clinical presentation and saccade impairments in JHD. Saccade abnormalities reported in our study are mostly consistent with those reported in adult HD, with one exception. It was noted in patients with HD that the mean latency in reflexive saccades with gap was shorter than in the overlap task [8]. The same gap-overlap effect on saccade latency was observed in healthy subjects. In our study, the mean latency in both tasks was significantly increased in JHD patients and the difference between results of these tests was insignificant compared to a significant difference in the control group. It could indicate that parietal structures in the brain, which seem to mediate the gap-overlap effect on saccade latencies, are more affected in JHD patients.

Our results showed that with increased clinical severity, JHD patients presented a significant increase in eye movement latencies for the gap task, therefore the assessment of the latency in reflexive saccades with gap seems to be useful to track clinical symptoms in JHD patients. Among the cognitive measures, we found that VFT, which assesses working memory, correlated significantly with saccade abnormalities. Verbal Fluency Test does not require motor functions and we expected that tests which need visuomotor integration and planning (SDMT and SCWT) would be more sensitive. Nevertheless, the deterioration of cognitive performance for VFT, SDMT and SCWT in JHD was already reported [22] and we showed correlation between VFT and saccade abnormalities.

## Conflict of interest

None declared.

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None declared.

## Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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